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# Attenuation of the vagolytic effect of atropine during high thoracic epidural anesthesia by heart rate fluctuation analysis

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**Abstract:** Fifteen surgical patients received an epidural injection of 12 ml of 1.5% lidocaine through a catheter placed at C7-T1, followed by further injection as required. An intravenous bolus of 0.5 mg of atropine sulfate was administered simultaneously with the initial epidural injection. The high- (HFC: 0.15–0.4 Hz) and low-frequency components (LFC: 0.05–0.15 Hz) of the power spectrum of heart rate fluctuation, and the LFC/HFC ratio were calculated. At 30 min after the initial lidocaine and atropine injection, the HFC decreased to 21% of the baseline value and the LFC decreased to 11%. At 90 min, the HFC showed gradual recovery to 69% whereas the LFC remained low (22%). These results indicate that 0.5 mg of intravenous atropine reduces the autonomic imbalance that occurs under high thoracic epidural anesthesia, but its duration is too short to be effective throughout the course of anesthesia.

**Key words:** High thoracic epidural anesthesia, R-R interval, Power spectral analysis, Autonomic imbalance

## Introduction

Because of anatomical differences between the cardiac sympathetic nerve and the vagus nerve, it has been speculated that the sympathetic nerves alone are blocked by high thoracic epidural anesthesia, resulting in an imbalance of the autonomic influences on the heart. We have previously demonstrated, using analysis of heart rate fluctuation, that mild vagotonia occurs with high thoracic epidural anesthesia and that this can be partially antagonized by intravenous atropine [1]. However, that study did not examine the successive changes occurring during the whole clinical course of high thoracic epidural anesthesia. Thus, it was not clarified whether the vagolytic effect of atropine was attenuated over time, resulting in recurrence of the imbalance in autonomic activity.

In the present study, we used heart rate fluctuation analysis to quantitatively evaluate sympathetic and parasympathetic nervous activity in surgical patients undergoing high thoracic epidural anesthesia.

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## Patients and methods

### *Patients*

After obtaining the approval of our Institutional Ethics Committee, we studied 15 patients (40.6 ± 7.5 [SD] years old and 61.1 ± 4.3 kg body weight) who were scheduled for orthopedic or plastic surgery of the upper extremities under high thoracic epidural anesthesia. All of these patients were ASA physical status 1–2 and in normal sinus rhythm. They had no signs of autonomic dysfunction or cardiovascular disease detected by clinical laboratory tests or preanesthetic interview, and none of them were on chronic medications. Informed consent was obtained from all patients.

### *Procedures*

One hour before entering the operating room, the patients were premedicated with oral triazolam (0.25 mg) and with intramuscular pentazocine (15 mg) and famotidine (20 mg).

In the operating room, lead II of the electrocardiogram (ECG) was monitored (Lifescope 12, Nihon Kohden, Tokyo, Japan) and the waveforms were fed into an on-line microcomputer (NEC 9801VX, NEC, Tokyo, Japan) via a waveform regulator (Nihon Kohden) to allow measurement of the R-R interval with a time resolution of 0.5 ms. R-R interval data were

stored on the computer. The details of R-R interval measurement have been reported previously [1,2].

An intravenous cannula was introduced for the infusion of Ringer's lactate solution and drug administration. Blood pressure was determined by the cuff method with a noninvasive automatic sphygmomanometer (Lifescope 12, Nihon Kohden).

The patient was then placed in the lateral recumbent position. The epidural space was punctured at C7-T1 using a 17 G Tuohy needle, through which an epidural catheter was introduced 8 cm from the skin. The patient was then returned to the supine position and 12 ml of 1.5% lidocaine was injected through the catheter for about 1 min. At the same time, 0.5 mg of atropine sulfate was injected intravenously. The analgesic level was determined at 15 min after injection by the pinprick method. After the C4-T5 dermatomes were confirmed to be analgesic, surgery was commenced. Subsequently, 6–7 ml of 1.5% lidocaine was injected every 40–50 min to maintain anesthesia.

All patients were operated on in the supine position under spontaneous respiration, receiving 3 l/min of oxygen through a face mask. For sedation, 15 mg of pentazocine and 0.5–0.75 mg of flunitrazepam was administered intravenously at 15–20 min after the initiation of epidural anesthesia.

### *ECG sampling time points*

The ECG was sampled for 4 min at each of the following times after the concomitant injection of epidural lidocaine and intravenous atropine: immediately before the injection (baseline) and at 5 min (post-atropine baseline), 30 min, 60 min, and 90 min. Blood pressure was determined simultaneously at all these time points.

### *Heart rate fluctuation analysis*

R-R interval data were stored on the computer and analyzed later. The mean R-R interval was calculated from all R-R interval data sample during each 4-min period and the R-R interval data for each period were transfered to serial-correlated data (i.e., individual R-R intervals on the ordinate and cumulative R-R intervals on the abscissa). Then, the serial-correlated data were re-sampled at 5 Hz using Lagrangian interpolation, and the 50th to 1074th data (1024 segments) were chosen for spectral analysis. To accurately detect the spectrum, we used Hunning window fitting. Power spectral analysis was carried out by fast Fourier analysis. The power spectrum of the heart rate forms three peaks: one below 0.05 Hz, one at around 0.1 Hz, and one at around 0.25 Hz [3–5]. We took the spectrum from 0.05–0.15 Hz as the low-frequency component (LFC) and that from 0.15–0.4 Hz as the high-frequency component (HFC), and calculated the respective band areas as the power of each component. The unit of area was $ms^2$. The LFC/HFC ratio was then calculated for each area as an index of sympathovagal interaction [4].

Measured values were expressed in absolute terms, and percent changes from the preanesthetic level (baseline) were calculated. Additional comparisons were made between the 5-min and the 30-, 60- and 90-min values. Wilcoxon's rank-sum test was used for statistical analysis and $P < 0.05$ was considered significant.

## Results

The mean operating time was 97.4 ± 7.6 min. Table 1 shows the serial changes in blood pressure and heart rate fluctuation during the clinical course of high thoracic epidural anesthesia.

Systolic blood pressure was decreased at 5 and 30 min ($P < 0.05$) compared with the baseline value, while the diastolic blood pressure did not change throughout the course of anesthesia. The mean R-R interval did not show significant changes compared with the baseline value, while it showed significant prolongation at 60 and 90 min compared with the 5-min value (Fig. 1).

**Table 1.** Serial changes in blood pressure, R-R interval, and power spectrum of R-R interval after the initiation of high thoracic epidural anesthesia

| | Baseline | 5 min | 30 min | 60 min | 90 min |
|---|---|---|---|---|---|
| SBP (mmHg) | 125.2 ± 5.5 | 119.6 ± 4.6* | 112.1 ± 4.4* | 112.4 ± 4.4 | 119.8 ± 5.1 |
| DBP (mmHg) | 70.1 ± 3.1 | 67.6 ± 3.0 | 65.2 ± 3.5 | 65.2 ± 3.5 | 68.1 ± 2.9 |
| R-R interval (ms) | 814.6 ± 41.7 | 786.4 ± 41.8 | 811.3 ± 44.0 | 856.3 ± 32.6† | 853.5 ± 40.0† |
| HFC power ($ms^2$) | 0.82 ± 0.11 | 0.33 ± 0.06** | 0.14 ± 0.06** | 0.36 ± 0.05** | 0.56 ± 0.06† |
| LFC power ($ms^2$) | 0.65 ± 0.08 | 0.15 ± 0.02** | 0.06 ± 0.04**† | 0.11 ± 0.02** | 0.13 ± 0.03** |
| LFC/HFC ratio | 0.88 ± 0.09 | 0.49 ± 0.07 | 0.41 ± 0.08* | 0.39 ± 0.08* | 0.39 ± 0.06* |

Values are mean ± SE.
* $P < 0.05$, ** $P < 0.01$ *vs* baseline; † $P < 0.05$ *vs* 5-min values
SBP, systolic blood pressure; DBP, diastolic blood pressure; HFC, high-frequency component; LFC, low-frequency component.

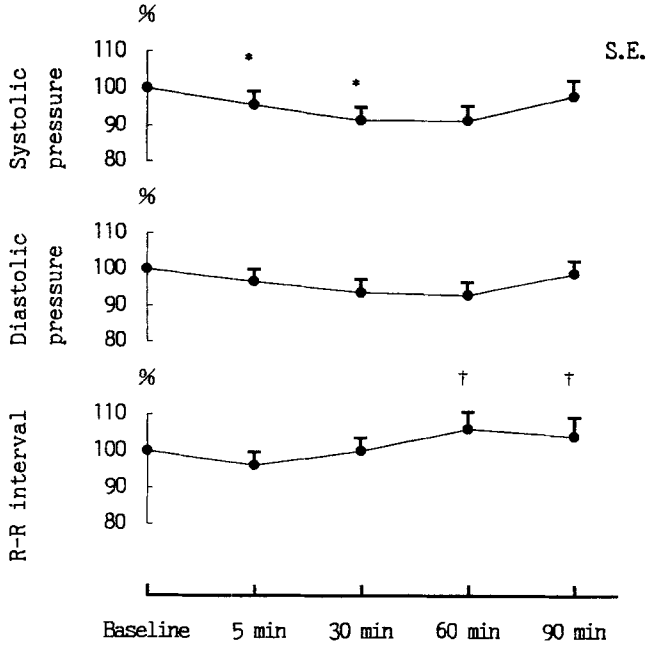


**Fig. 1.** Percent changes in systolic blood pressure (*upper*), diastolic blood pressure (*middle*), and R-R interval (*lower*) after the initiation of high thoracic epidural anesthesia

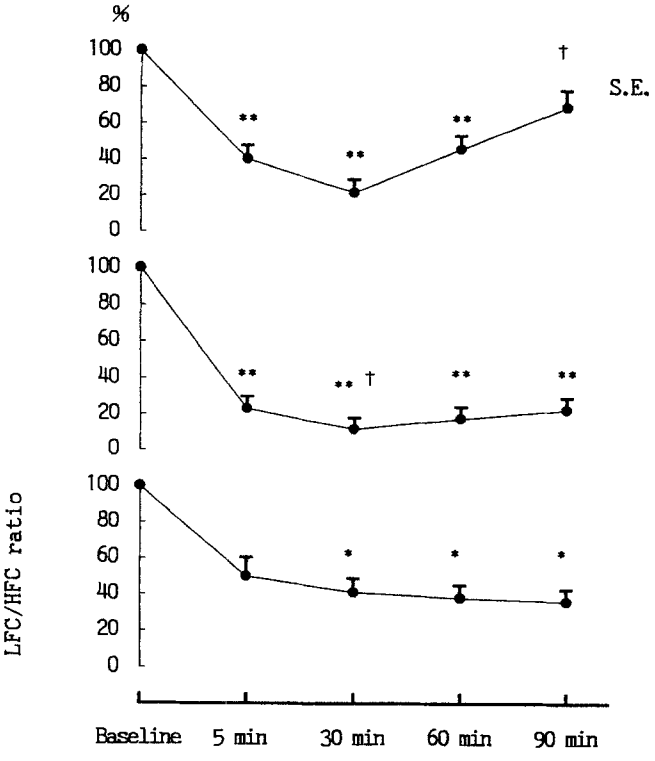


**Fig. 2.** Percent changes in the high-frequency component (HFC: *upper*), the low-frequency component (LFC: *middle*), and the LFC/HFC ratio (*lower*) after initiation of high thoracic epidural anesthesia

The HFC decreased to 40% (mean) of the baseline value at 5 min ($P < 0.01$). The 30-min value was 21% of the baseline value ($P < 0.01$), i.e., there was a further decrease from the 5-min value ($P < 0.05$). The 60-min value was 43% of the baseline value ($P < 0.05$) and the 90-min value was 69% of baseline, showing an increase ($P < 0.05$) from the 5-min value (upper column, Fig. 2).

The LFC decreased to 23% of the baseline value at 5 min ($P < 0.01$). The 30-min value was 11% of baseline, the lowest value ($P < 0.01$), showing a further decrease from the 5-min value ($P < 0.05$). The 60- and 90-min values were 17% and 22% of the baseline level, respectively. Although the LFC tended to recover slightly after 30 min, it still remained significantly lower than at the baseline (middle column, Fig. 2).

The LFC/HFC ratio was decreased to 51% of the baseline value at 5 min, but this change was not significant. The 30-min value was 41% of baseline ($P < 0.05$). While the 60- and 90-min values were decreased further to 38% and 36% of baseline, respectively (both $P < 0.05$). Compared with the 5-min value, however, there were no significant changes at 30, 60 and 90 min (lower column, Fig. 2).

## Discussion

In this study, using heart rate fluctuation analysis, we demonstrated quantitative changes of autonomic activity during clinical high thoracic epidural anesthesia. The vagolytic effect of 0.5 mg of atropine administered concomitantly with the initiation of epidural anesthesia was not sufficient to overcome the imbalance, and its duration was too short to be effective throughout the course of the epidural anesthesia.

As this study was conducted during clinical surgery, we could not avoid the use of anesthetic premedication and intraoperative sedation that might also affect autonomic activity. Oral triazolam might be expected to cause slight inhibition of sympathetic activity through its sedative effect [6]. Flunitrazepam is reported to have little effect on the circulatory system at routine clinical doses, with no significant effect shown on heart rate [7]. However, this drug does inhibit the circulatory responses to surgical stimulation [8]. In contrast, small doses of pentazocine stimulate sympathetic activity [9]. Therefore, we cannot exclude the possibility that the drugs given immediately before surgery may have affected autonomic activity.

The systemic effect of lidocaine (absorbed from the epidural veins) on heart rate fluctuations may also be relevant. When present at significant concentrations in the plasma, lidocaine suppresses the cough reflex [10] and decreases reflex-mediated bradycardia following phenylephrine injection [11]. Although the plasma con-

centration of lidocaine was not measured in this study, it seems likely that plasma levels were reached which could influence the autonomic imbalance. We will therefore discuss autonomic imbalance as a total clinical phenomenon, including any of the above influences.

The heart rate fluctuates rhythmically even during normal sinus rhythm. The LFC and HFC determined by power spectral analysis in this study have been pharmacologically and physiologically examined by many investigators [3–5]. The HFC represents respiratory sinus arrhythmia and is interpreted as an indicator of vagal activity. Scheffer reported that the HFC is caused by respiratory-induced blood pressure fluctuations which are mediated by the baroreflex arc via the vagus nerve [12]. More recently, Shimizu et al., using $CO_2$ challenge under controlled ventilation, demonstrated that the HFC is not solely due to respiration-induced blood pressure fluctuations [13].

The LFC is synchronized with a sympathetically induced rhythmic blood pressure fluctuation known as the Mayer wave [3–5]. Kawamoto et al. reported that spinal anesthesia to a sensory level of T4-T7 decreased the LFC [14]. Scheffer proposed that the LFC was produced by sympathetic modulation of vasomotor tone rather than by sympathetic innervation to the heart [12]. The LFC has been shown to be suppressed by atropine [1,5], suggesting that vagal activity participates in the LFC of the heart rate fluctuation. In our previous study [1], both the HFC and LFC tended to increase with epidural blockade of cold sensation of C4-T5. With epidural anesthesia of this level, sympathetic vasomotor activity should remain unblocked. The increase of LFC in our previous study may thus be explained by a vagotonic effect along with the preservation of sympathetic vasomotion.

Thirty minutes after injection of lidocaine and atropine, both the HFC and LFC values reached the lowest values and the LFC/HFC ratio was shifted predominantly toward the HFC. Pomeranz et al. [5] reported that the HFC was decreased to 8% of the baseline level by 0.03 mg/kg of intravenous atropine. In the present study, the mild decrease in HFC compared with their reported change indicates that the routine clinical dose (0.5 mg) of atropine was insufficient to achieve complete vagolysis. The prominent decreases in the LFC rather than the HFC indicated suppression of sympathetic vasomotor activity in addition to the effect of atropine on the LFC. The C4-T5 dermatomes were confirmed to be analgesic in the present study, suggesting that the level of sympathetic blockade was broader than in the previous study. Comparing the results of our two studies employing high thoracic epidural anesthesia, the difference in the level of sympathetic blockade influences the net effect on autonomic activity.

At 60 min, the HFC showed an increase from the 30-min value, while the LFC/HFC ratio decreased further during the anesthesia. Compared with the 5-min value (post-atropine baseline), the mean R-R interval was prolonged significantly at 60 and 90 min. This indicates attenuation of the vagolytic effect of atropine during continuous blockade of sympathetic activity, with the difference in the blockade of sympathetic and vagal activity becoming more apparent at 90 min. These findings strongly suggest that sympathetic activity was dissociated from vagal activity, resulting in recurrence of the imbalance in autonomic activity.

Although the elimination half-life of atropine is reported to be roughly 4.1 h [15], its suppressive effect on vagal activity showed a decrease at 60 min after intravenous injection. If the dose administered was insufficient, then the blood concentration of atropine would decrease below the effective level and thus shorten the duration of action. Jansen and Dellinger gave an intravenous injection of 14 μg/kg of atropine to rhesus monkeys and found that respiratory arrhythmia reappeared 90 min later, whereas monkeys administered 140 μg/kg did not show complete recovery of respiratory arrhythmia after even 180 min [16]. Our findings and those of this animal study suggest that subsequent intermittent or continuous administration of atropine should be continued during the entire course of high thoracic epidural anesthesia to maintain a vagolytic state.

Cardiac sympathetic denervation due to high thoracic epidural anesthesia has been reported to cause no major impairment of hemodynamic function [17,18]. In this study, we also found no remarkable changes in blood pressure or the R-R interval. Hogan et al. reported that a marked decrease of splanchnic sympathetic activity causes major hemodynamic impairment [19]. Thus, the impairment of hemodynamic function during epidural anesthesia should be attributed to splanchnic sympathectomy rather than blockade of cardiac sympathetic activity.

However, our assessment using heart rate fluctuations revealed a variety of changes in autonomic function. Several cases of intraoperative coronary artery spasm under epidural anesthesia have been reported [20,21]. Yasue et al. demonstrated that coronary artery spasm is induced by acetylcholine, indicating a possible role of the parasympathetic nervous system in the pathogenesis of coronary spasm [22]. If the vagolytic effect of atropine is decreased under sympathetic denervation, the acetylcholine sensitivity of the heart would increase, affecting both cardiac performance and coronary perfusion.

In conclusion, we found that relative vagotonia occurred with high thoracic epidural anesthesia, and that the vagolytic effect of a bolus of 0.5 mg atropine was not

sufficient to counteract this. To counteract vagotonia for the entire duration of high thoracic epidural anesthesia, additional doses of atropine are necessary.

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